PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Commissioner
US Department of Commerce
United States Patent and Trademark Office, PCT
2011 South Clark Place Room CP2/5C24
Arlington, VA 22202
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 01 June 2001 (01.06.01)	
International application No. PCT/GB00/03489	**Applicant's or agent's file reference** WPP81229
International filing date (day/month/year) 11 September 2000 (11.09.00)	**Priority date** (day/month/year) 10 September 1999 (10.09.99)
Applicant CIMINO, Guido et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

09 April 2001 (09.04.01)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer

Olivia TEFY

Telephone No.: (41-22) 338.83.38

Copy for the Elected Office (EO/US)

PCT/GB00/03489

PATENT COOPERATION TREATY

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From the INTERNATIONAL BUREAU

To:

RUFFLES, Graham, Keith
Marks & Clerk
57-60 Lincoln's Inn Fields
London WC2A 3LS
ROYAUME-UNI

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and Administrative Instructions, Section 422)

Date of mailing (day/month/year) 19 June 2001 (19.06.01)	
Applicant's or agent's file reference WPP81229	**IMPORTANT NOTIFICATION**
International application No. PCT/GB00/03489	**International filing date** (day/month/year) 11 September 2000 (11.09.00)

1. The following indications appeared on record concerning:

[X] the applicant [X] the inventor [ ] the agent [ ] the common representative

Name and Address	State of Nationality	State of Residence
	IN	IN
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

[X] the person [ ] the name [ ] the address [ ] the nationality [ ] the residence

Name and Address	State of Nationality	State of Residence
NAIK, Chandrakant, Govind National Institute of Oceanography Dona Paula, Goa 403 004 India	IN	IN
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

3. Further observations, if necessary:
Additional applicant/inventor for the US only.

4. A copy of this notification has been sent to:

[X] the receiving Office
[ ] the International Searching Authority
[X] the International Preliminary Examining Authority
[ ] the designated Offices concerned
[X] the elected Offices concerned
[ ] other:

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer Maria Victoria CORTIELLO
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

Form PCT/IB/306 (March 1994)

004095228

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

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NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

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Arlington, VA 22202
ETATS-UNIS D'AMERIQUE

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Date of mailing (day/month/year) 01 June 2001 (01.06.01)	
International application No. PCT/GB00/03489	**Applicant's or agent's file reference** WPP81229
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Applicant CIMINO, Guido et al	

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[X] in the demand filed with the International Preliminary Examining Authority on:

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2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer

Olivia TEFY

Telephone No.: (41-22) 338.83.38

INTERNATIONAL SEARCH REPORT

[redacted] tal Application No
[redacted]/GB 00/03489

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D471/18 . A61K31/4995 A61P35/00 //(C07D471/18,241:00, 221:00,221:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	HE, HAI YIN ET AL: "Renieramycins E and F from the sponge Reniera sp.: reassignment of the stereochemistry of the renieramycins" J. ORG. CHEM. (1989), 54(24), 5822-4 , XP002162279 compound 15	1
A	US 5 023 184 A (REICHENBACH HANS ET AL) 11 June 1991 (1991-06-11) abstract	1,4

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

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"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
7 March 2001	23/03/2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Alfaro Faus, I

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Intern[illegible]al Application No
PCT[illegible] 00/03489

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	FONTANA, A. ET AL: "A new antitumor isoquinoline alkaloid from the marine nudibranch Jorunna funebris" TETRAHEDRON (2000), 56(37), 7305-7308 , XP002162280 compound 3; page 7308, column 2, cytotoxicity assay	1,4

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Interna[redacted]al Application No
P[redacted]GB 00/03489

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5023184 A	11-06-1991	AU 628643 B	17-09-1992
		AU 6231690 A	13-12-1990
		AU 605783 B	24-01-1991
		AU 7687487 A	18-02-1988
		DK 423987 A	16-02-1988
		EP 0262085 A	30-03-1988
		IL 83532 A	29-03-1992
		JP 63049092 A	01-03-1988
		NZ 221442 A	28-08-1990
		PT 85535 A,B	01-09-1987
		ZA 8706030 A	30-03-1988

Part of #7 10/070561

INTERNATIONAL SEARCH REPORT

International Application No PCT/GB 00/03489

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D471/18 A61K31/4995 A61P35/00 //(C07D471/18,241:00, 221:00.221:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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A	US 5 023 184 A (REICHENBACH HANS ET AL) 11 June 1991 (1991-06-11) abstract —	1,4

-/--

[X] Further documents are listed in the continuation of box C. [X] Patent family members are listed in annex.

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"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
7 March 2001	23/03/2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Alfaro Faus, I

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

PCT/GB 00/03489

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	FONTANA, A. ET AL: "A new antitumor isoquinoline alkaloid from the marine nudibranch Jorunna funebris" TETRAHEDRON (2000), 56(37), 7305-7308 , XP002162280 compound 3; page 7308, column 2, cytotoxicity assay	1,4

1

INTERNATIONAL SEARCH REPORT

PCT/GB 00/03489

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5023184 A	11-06-1991	AU 628643 B	17-09-1992
		AU 6231690 A	13-12-1990
		AU 605783 B	24-01-1991
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		DK 423987 A	16-02-1988
		EP 0262085 A	30-03-1988
		IL 83532 A	29-03-1992
		JP 63049092 A	01-03-1988
		NZ 221442 A	28-08-1990
		PT 85535 A,B	01-09-1987
		ZA 8706030 A	30-03-1988

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
22 March 2001 (22.03.2001)

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(10) International Publication Number
WO 01/19824 A2

(51) International Patent Classification[7]: C07D 471/18, A61K 31/4995, A61P 35/00 // (C07D 471/18, 241:00, 221:00, 221:00)

(21) International Application Number: PCT/GB00/03489

(22) International Filing Date:
11 September 2000 (11.09.2000)

(25) Filing Language: English

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(30) Priority Data:
9921477.7 10 September 1999 (10.09.1999) GB

(71) Applicant *(for all designated States except US)*: INSTITUTO BIOMAR, S.A. [ES/ES]; Polígono Industrial, Edificio CEI, Mod. 2.02 y 2.03, E-24231 Onzonilla (Leon) (ES).

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(75) Inventors/Applicants *(for US only)*: CIMINO, Guido [IT/IT]; Instituto per la Chimica di Molecole di Interesse Biologico (ICMIB) del CNR, Via Toiano, 6, I-80072 Arco Felice (IT). FONTANA, Angelo [IT/IT]; Instituto per la Chimica di Molecole di Interesse Biologico (ICMIB) del CNR, Via Toiano, 6, I-80072 Arco Felice (IT). GARCIA GRAVALOS, Dolores [ES/ES]; Pharma Mar, S.A., Calle de la Calera, 3, Poligono Industrial de Tres Cantos, Tres Cantos, E-28760 Madrid (ES). WAHIDULLA, Solimabi [/IT]; Instituto per la Chimica di Molecole di Interesse, Biologico (ICMIB), del CNR, Via Toiano 6, Arco Felice (NA) 80072 (IT).

(74) Agent: RUFFLES, Graham, Keith; Marks & Clerk, 57-60 Lincoln's Inn Fields, London WC2A 3LS (GB).

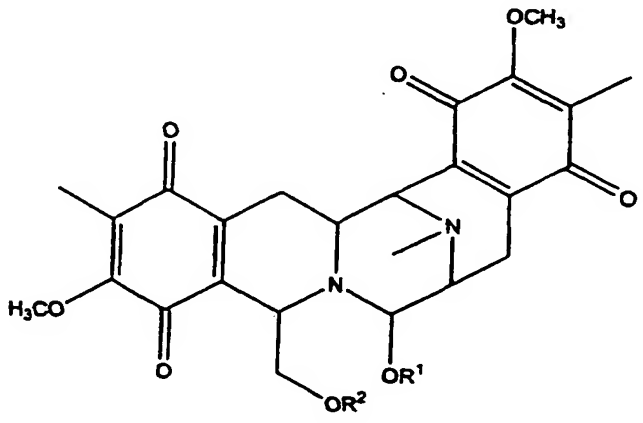
(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *Without international search report and to be republished upon receipt of that report.*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: NEW ACTIVE MARINE ALKALOIDS



(I)

(57) Abstract: New antitumour alkaloids of general formula (I) where R^1 is hydrogen, alkyl or acyl and R^2 is hydrogen or acyl, include jorumycin, where R^1 is hydrogen and R^2 is acetyl, extracted from the mollusc *Jorunna funebris*.

WO 01/19824 A2

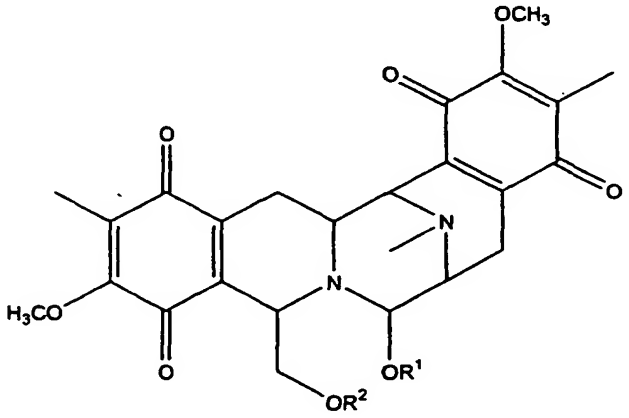
NEW ACTIVE MARINE ALKALOIDS

The present invention relates to new active alkaloids and in particular to an alkaloid isolated from the mollusc *Jorunna funebris*.

Marine organisms, especially soft corals, sponges and tunicates, provide many secondary metabolites and exhibit a varying degree of biological activity (Faulkner, D.J. *Nat. Prod. Reports.*, **1999**, *16*, 155-198 and references cited therein).

Summary of the Invention

The present invention provides alkaloids having the following formula (I):



wherein R^1 is selected from the group consisting of hydrogen, lower alkyl group and lower acyl group and R^2 is selected from the group consisting of hydrogen and lower acyl. In the definitions of the groups in formula (I), the lower alkyl group and the lower alkyl moiety of the lower acyl are typically a straight-chain or branched alkyl group having 1 to 6 carbon atoms such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, neopentyl and hexyl.

Jorumycin exhibits antitumour activity. In particular, Jorumycin exhibits antitumour activity against cell lines derived from human solid tumours, such as human lung

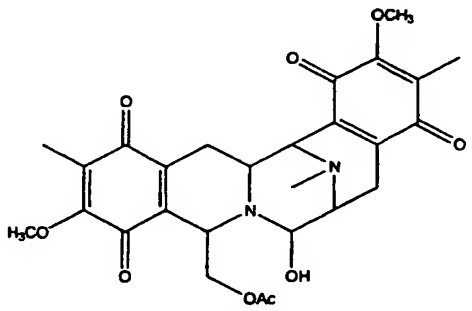
carcinoma, human colon carcinoma and human melanoma, and the like. It is active against other tumour cell lines, like leukaemia and lymphoma.

The present invention also provides a method of treating a mammal affected by a malignant tumour sensitive to a compound of the formula (I), which comprises administering a therapeutically effective amount of the compound of the formula (I), or a pharmaceutical composition thereof.

The present invention further provides pharmaceutical compositions which contain as active ingredient a compound of the formula (I), as well as a process for its preparation.

The present invention also provides use of the compound of formula (I) in the preparation of a medicament for the treatment of prophylaxis of tumours.

More particularly, the present invention relates to Jorumycin (R^1=H and R^2=Ac in formula (I)), extracted and isolated from the mollusc *Jorunna funebris*. Jorumycin is of the formula:



Jorumycin free from other compounds occurring in the mollusc is provided, as well as substantially pure jorumycin. A further aspect of the invention is a method for preparing the compound Jorumycin (R^1=H and R^2=Ac in the formula (I)), which comprises extraction and isolation from the mollusc *Jorunna funebris*.

Preferred Embodiments of the Invention

Examples of pharmaceutical compositions include any solid (tablets, pills, capsules,

granules, etc.) or liquid (solutions, suspensions or emulsions) with suitable formulation of oral, topical, parenteral or other administration, and they may contain the pure compound or in combination with any carrier or other pharmacologically active compounds. These compositions may need to be sterile when administered parenterally.

The correct dosage of a pharmaceutical composition comprising compounds of the formula (I), will vary according to the pharmaceutical formulation, the mode of application, and the particular situs, host and tumour being treated. Other factors like age, body weight, sex, diet, time of administration, rate of excretion, condition of the host, drug combinations, reaction sensitivity and severity of the disease shall be taken into account. Administration can be carried out continuously or periodically within the maximum tolerated dose.

Antitumour Activity

Cells were maintained in logarithmic phase of growth in Eagle's Minimum Essential Medium, with Earle's Balanced Salts, with 2.0 mM L-glutamine, with non-essential amino acids, without sodium bicarbonate (EMEM/neaa); supplemented with 10% Fetal Calf Serum (FCS), 10^{-2} M sodium bicarbonate and 0.1 g/l penicillin-G + streptomycin sulfate.

A screening procedure has been carried out to determine and compare the antitumour activity of these compounds, using an adapted form of the method described by Bergeron et al (Raymond J Bergeron, Paul F Cavanaugh, Jr, Steven J Kline, Robert G Hughes, Jr, Gary T Elliot and Carl W Porter. Antineoplastic and antiherpetic activity of spermidine catecholamide iron chelators. *Biochem. Bioph. Res. Comm.* **1984**, *121*, 848-854). The antitumour cells employed were P-388 (suspension culture of a lymphoid neoplasm from DBA/2 mouse), A-549 (monolayer culture of a human lung carcinoma), HT-29 (monolayer culture of a human colon carcinoma) and MEL-28 (monolayer culture of a human melanoma).

P-388 cells were seeded into 16 mm wells at 1 x 10^4 cells per well in 1 ml aliquots of MEM 5FCS containing the indicated concentration of drug. A separate set of cultures without drug was seeded as control growth to ensure that cells remained in exponential phase of growth. All determinations were carried out in duplicate. After three days of incubation at 37°C, 10% CO_2 in a 98% humid atmosphere, an approximately IC_{50} was determined by comparing the growth in wells with drug to the growth in wells control.

A-549, HT-29 and MEL-28 cells were seeded into 16 mm wells at 2 x 10^4 cells per well in 1 ml aliquots of MEM 10FCS containing the indicated concentration of drug. A separate set of cultures without drug was seeded as control growth to ensure that cells remained in exponential phase of growth. All determinations were carried out in duplicate. After three days of incubation at 37°C, 10% CO_2 in a 98% humid atmosphere, the wells were stained with 0.1% Crystal Violet. An approximately IC_{50} was determined by comparing the growth in wells with drug to the growth in wells control.

The results are given in the following table:

	$IC_{50}(\mu M)$			
	P-388	**A-549**	**HT-29**	**MEL-28**
Jorumycin	0.02	0.02	0.02	0.02

Antitumour Activity

Jorumycin showed also activity against Gram-positive bacteria (*Staphylococcus* and others).

Extraction and Isolation

Jorumycin was isolated from the mollusc *Jorunna funebris* (Mollusca: Nudibranchia:

Doridina: Kentrodorididae) collected off Mandapam (India) in April 1998. The product is present in the extract of both the mucus and mantle of the nudibranch. In a typical procedure, the frozen biological sample (mucus or animal body) was extracted with acetone. After removing the organic solvent at reduced pressure the residue was partitioned between water (15 ml) and ethyl acetate. The water phase was extracted for three times with ethyl acetate (total 34 ml). The oily residue obtained by removing of the organic solvent at reduced pressure was fractioned by Sephadex LH-20 chromatography following the elution of the extract components by SiO_2-TLC (CHC_{13}/MeOH 95:5, Rf = 0.4). The final purification of Jorumycin was obtained by sequential SiO2 chromatographies ($CHCl_3$/MeOH) and HPLC (Sherisorb S5W analytical column, isocratic elution with: n-hexane/CHC_{13}/TEA 90:10:10, detector: Waters R401 differential refractometer). The product is soluble in CHC_{13}, CH_2Cl_2, MeOH. It is highly unstable in acid and basic media.

Jorumycin:

($C_{27}H_{30}N_2O_9$);

$[\alpha]_D$= -57° (*c* 0.05 $CHCl_3$);

IR (liquid film) 3310, 1731, 1700 cm^{-1};

UV (MeOH) 268 nm (ε=15000);

^{1}H-NMR ($CDCl_3$) δ 1.25 (m, 1H), 1.75 (s, 3H), 1.93 (s, 3H), 1.96 (s, 3H), 2.24 (d, 1H, J=20.1 Hz), 2.26 (s, 3H), 2.65 (dd, 1H, J=20.1 and 7.3 Hz), 2.84 (dd, 1H, J=16.7 and 2.1 Hz) 3.16 (bdt, 1H, J=12.0, 2.7 and 2.7 Hz). 3.18 (bs, 1H), 3.82 (dd, 1H, J=11.2 and 3.5 Hz), 3.90 (bs, 1H), 3.98 (s, 3H), 4.00 (bs, 3H), 4.36 (bm, 1H), 4.40 (bs, 1H), 4.42 (dd, 1H, J=11.2 and 3.7 Hz);

^{13}C-NMR ($CDCl_3$) δ 185.8 (s), 181.3 (s), 170.0 (s), 155.7 (s), 155.0 (s), 141.9 (s), 141.7 (s), 137.2 (s), 128.8 (s), 128.4 (s), 113.8 (s), 109.4 (s), 83.0 (d), 65.2 (t), 61.0 (d), 57.7 (d), 56.1 (d), 54.4 (d), 52.6 (d), 41.3 (q), 25.5 (t), 20.7 (q), 20.6 (t), 8.8 (q), 8.7 (q);ESMS (*m/z*) 526 (20, M+), 508 (100, M-H_2O), 494 (10, M-32);

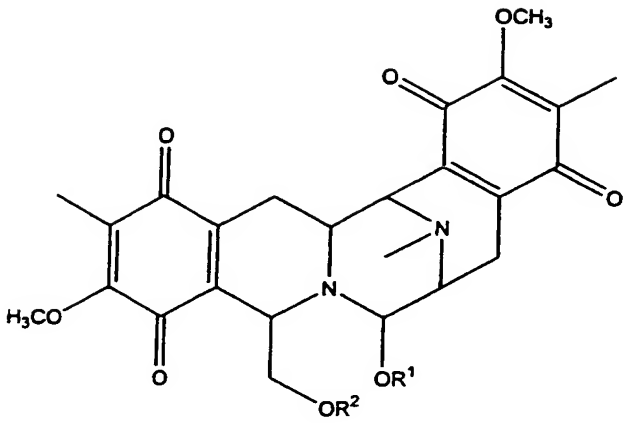
HRESMS (*m/z*) 508.189 (Δ + 5 mmu).

Other compounds of formula (I) may readily be prepared by chemical synthesis or

hemisynthesis.

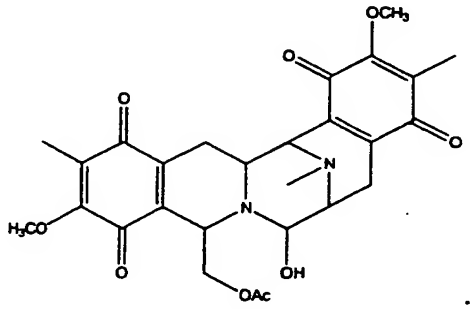
CLAIMS:

1. A compound the following formula (I):



wherein R^1 is selected from the group consisting of hydrogen, lower alkyl group and lower acyl group and R^2 is selected from the group consisting of hydrogen and lower acyl.

2. A compound according to claim 1, which is jorumycin, where R^1 is H and R^2 is Ac:



3. A method of treating a mammal affected by a malignant tumour sensitive to a compound of the formula (I) of claim 1, which comprises administering a therapeutically effective amount of the compound of the formula (I), or a pharmaceutical composition thereof.

4. A pharmaceutical composition comprising a compound of the formula (I) of claim 1, together with a pharmaceutically acceptable carrier.

5. A method for preparing the compound of claim 2, which comprises extraction and isolation from the mollusc *Jorunna funebris*.

6. The use of a compound of formula (I) of claim 1 in the preparation of a medicament for the treatment of tumours.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

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PCT

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(21) International Application Number: PCT/GB00/03489

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(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

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Published:
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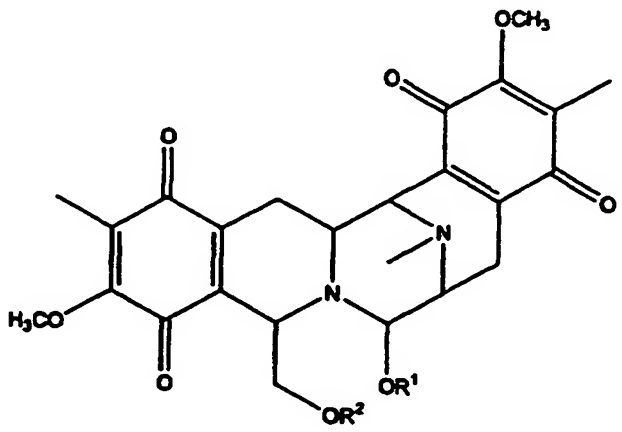
27 September 2001

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: NEW ACTIVE MARINE ALKALOIDS



(I)

(57) Abstract: New antitumour alkaloids f general formula (I) where R^1 is hydrogen, alkyl or acyl and R^2 is hydrogen or acyl, include jorumycin, where R^1 is hydrogen and R^2 is acetyl, extracted from the mollusc *Jorunna funebris*.

WO 01/19824 A3

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
WPP81229		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB00/03489	11/09/2000	10/09/1999
International Patent Classification (IPC) or national classification and IPC C07D471/18		
Applicant INSTITUTO BIOMAR, S.A. et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☒ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
09/04/2001	15.11.2001
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Rudolf, M Telephone No. +49 89 2399 8604

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB00/03489

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
Description, pages:

1-6 as originally filed

Claims, No.:

1-6 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 3.

because:

☒ the said international application, or the said claims Nos. 3 with respect to industrial applicability relate to the following subject matter which does not require an international preliminary examination (*specify*):
see separate sheet

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos. .

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	2,3,5,6
	No:	Claims	1,4
Inventive step (IS)	Yes:	Claims	2,3,5,6
	No:	Claims	1,4
Industrial applicability (IA)	Yes:	Claims	1,2,4-6

No: Claims

2. Citations and explanations
see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:
see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

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To section III:

Claim 3 relates to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

To section V:

The following documents are cited in the search report:

D1: HE, HAI YIN ET AL: 'Renieramycins E and F from the sponge Reniera sp.: reassignment of the stereochemistry of the renieramycins' J. ORG. CHEM. (1989), 54(24), 5822-4 , XP002162279

D2: US-A-5 023 184 (REICHENBACH HANS ET AL) 11 June 1991 (1991-06-11)

D3: FONTANA, A. ET AL: 'A new antitumor isoquinoline alkaloid from the marine nudibranch Jorunna funebris' TETRAHEDRON (2000), 56(37), 7305-7308 , XP002162280

Compound 15 described in D1 falls within the scope of claim 1. The subject matter of claim 1 therefore is not new. Claim 4: The indication of purpose ("pharmaceutical composition") does not bring about novelty of the composition. Novelty could be established e.g. by excising compound 15 of D1 from the scope of the claims by means of a disclaimer.

The priority seems to be validly claimed, the document D3 referred to above appears to be not relevant for the present case.

The subject matter of claims 2,3,5,6 is therefore considered novel and inventive over the cited prior art.

For the assessment of the present claim 3 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can

also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

To section VII:

The document D1 disclosing a compound according to present formula I appears to be relevant prior art and should be cited in the application (Rule 5.1 a)ii) PCT).

To section VIII:

Claim 1: The terms "lower" in connection with carbon chain lengths should be clarified as found in the description (Art. 6 PCT).

PATENT COOPERATION TREA

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION** see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
WPP81229		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/GB 00/ 03489	11/09/2000	10/09/1999
Applicant		
INSTITUTO BIOMAR, S.A. et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 4 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

   a. With regard to the **language,** the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   [ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

   b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

   [ ] contained in the international application in written form.

   [ ] filed together with the international application in computer readable form.

   [ ] furnished subsequently to this Authority in written form.

   [ ] furnished subsequently to this Authority in computer readble form.

   [ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   [ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [X] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of invention is lacking** (see Box II).

4. With regard to the **title,**

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract,**

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. –

   [ ] as suggested by the applicant.

   [ ] because the applicant failed to suggest a figure.

   [ ] because this figure better characterizes the invention.

   [ ] None of the figures.